**Amendments to the Drawing:**

The drawing sheet appended in connection with the above-identified application containing Fig. 1 is being presented as a new formal drawing sheet to be substituted for the previously submitted drawing sheet. The drawing of Fig. 1 has been amended as per the suggestion of the Examiner, to show consistency for Δkin. Also appended to this amendment is an annotated copy of the previous drawing sheet which has been marked to show changes presented in the replacement sheet of the drawing.

The specific changes which have been made to Fig. 1 are the addition of an X in a kinase box for each of the schematic representations of the "Myr•p110/Δkin", "Myr•p110*/Δkin", "p110•H/Δkin", and "p110*•H/Δkin" constructs. The drawing amendments do not add new subject matter.

## REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-9 are currently being amended.

Claims 10-21 remain withdrawn.

This amendment changes claims in this application. A detailed listing of claims in the application is presented, each with an appropriately defined status identifier.

Drawing Objections

The objections to Fig. 1 have been addressed as noted above under "Amendments to the Drawing" to add an X in a kinase box of certain constructs having a Δkin. The amendments have been made for consistency and do not add new matter.

Claim Amendments

Claims 8 and 9 have each been amended to replace "A cell..." with "An isolated cell..." Support for such an amendment may be found throughout the specification, including at page 10, lines 3-4.

The remainder of the pending claims have also been amended to include the term "isolated", correct typographical errors, or otherwise clarify the claim language. Additionally, claims 1, 2, and 6 have been amended to more clearly define the derivatives or mutants of the nucleotide sequences claimed by referencing percent identity to native sequences. Support for the amendments may be found in the specification at page 6, lines 13-27.

The amendments to the claims do not add new matter and their entry is respectfully requested.

Claims 8-9

Claims 8-9 were objected to as encompassing non-elected embodiments and additionally were rejected under §101 as being directed to non-statutory subject matter. Claims 8-9 have been amended so as to specify that the transformed cell is isolated. Support for the term "isolated" can be found throughout the specification, e.g. at page 10, lines 3-4. With this amendment, claims 8-9 do not encompass non-elected matter nor impermissible subject matter. Applicant therefore requests that the objection to claims 8-9 and the rejection of claims 8-9 under §101 be removed.

Hu, Kapeller, Varticovski, and Aronheim

Claims 1-9 are directed to PI 3-kinase polynucleotide fusion constructs (and muteins and derivatives thereof).

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hu *et al., Science,* 268:100-102 (1995) (hereinafter "Hu"), in view of Kapeller *et al., BioEssays,* 16:565-576 (1994) (hereinafter "Kapeller"), Varticovski *et al., Mol. Cell. Biol.,* 11:1107-1113 (1991) (hereinafter "Varticovski"), and Aronheim *et al., Cell,* 78:949-961 (1994) (hereinafter "Aronheim"). Applicant respectfully disagrees with the Examiner's assessment because the cited art teaches away from the invention.

The Examiner cites Hu for disclosing "the p110* construct, which comprises DNA encoding the p110 subunit of PI 3-kinase and the iSH2 portion of the p85 subunit, attached via a "glycine kinker". According to the Examiner, "[t]he encoded protein is a constitutively active form of PI 3-kinase." Hu is also cited for disclosing "cells expressing p110*. Kapeller is cited for disclosing that "localization of PI 3-kinase to the plasma membrane" brings the enzyme into closer contact with its substrates. Varticovski is cited for disclosing that "PI 3-kinase must be localized to a membrane to work efficiently." Aronheim is cited for disclosing "methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for

myristoylation, farnesylation, and palmitoylation. The Examiner has concluded that it would have been obvious at the time of the invention "to modify the p110* construct of Hu et al. by adding DNA encoding membrane localization sequences as taught in the secondary references. Applicant respectfully disagrees.

Applicant notes that Hu actually teaches away from the instant invention, thus one of ordinary skill in the art would not have been motivated to combine the disclosures of Hu, Kapeller, Varticovski, and Aronheim. "A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading a reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See Monarch Knitting Machinery Corp. v. Sulzer, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998).

Although Kapeller, Varticovski, and Aronheim were known prior to the teachings of Hu, Hu teaches away from its combination with those disclosures. Each of Kapeller, Varticovski, and Aronheim discuss the importance of membrane localization for the *in vivo* activation of certain signaling proteins, *i.e.*, wild-type PI 3-kinase and Raf-1. See Kapeller, at page 571, right column, paragraph: "This result suggested that the cellular location of the oncoprotein-associated PtdIns 3-kinase activity may be important for transformation and that the lipid products of PtdsIns 3-kinase are essential in mediating its effects in mitogenesis." See also the abstract of Varticovski: "Myristoylation thus appears to be required to recruit PI 3-kinase activity to the plasma membrane for in vivo activation and correlates with the mitogenicity of the abl protein variants." The introduction of Aronheim is also relevant: "Activated GTP-bound Ras binds the cytoplasmic serine/threonine protein kinase Raf-1...leading to activation through translocation to the plasma membrane." In contrast, Hu, at page 102, middle column, first full paragraph, expressly discloses that the "only way" to activate PI 3-kinase, i.e., wild-type PI 3-kinase, "required" the use of tyrosine kinases. In his teachings, Hu expressed in cells a construct that was constitutively active in a growth factor-independent manner. Thus, by Hu's use of the limiting phrases "only way" in relation to activation and "required" in relation to tyrosine kinase,

Hu was not open to other modes of activation such as "myristoylation" as suggested by Varticovski, or GTP-bound Ras as suggested by Aronheim.

Moreover, Hu discloses a PI 3-kinase polynucleotide fusion construct comprising a p110 (domain)-linker-p85 (domain) that lacks any sort of membrane localization signal, is constitutively active, and does not require tyrosine kinases for activation. Thus, Hu teaches away from Applicant's invention and any use of myristoylation, palmitoylation, or farnesylation sequences to localize a PI 3-kinase fusion construct to the plasma membrane. *In re Fine,* 5 USPQ2d *1596,* 1599 (Fed. Cir. 1988) ("[e]rror to find obviousness where the references diverge and teach away from the invention at hand."). The rejection of claims 1-9 under § 103(a) is therefore in error.

Furthermore, Kapeller, Varticovski and Aronheim teach away from the claimed invention by disclosing factors, in addition to membrane localization, that are not found in the present invention but that are required for PI 3-Kinase activity. Kapeller, Varticovski, and Aronheim, teach away from any polynucleotide encoding any single protein, including a fusion protein, that would have PI 3-kinase activity due to membrane localization alone. In particular, Kapeller teaches away from the claimed polynucleotide fusion constructs by disclosing that other functional domains of p85, which are not components of the claimed polynucleotide fusion constructs (nor encoded by them), may be important for protein-protein interactions and may be required for PI 3-kinase activity, *e.g.*, SH2 and SH3 domains fall into this category. (Kapeller, at page 567, paragraph 2 to page 569, paragraph 1: "The SH2 and SH3 domains of p85 have been implicated in mediating protein-protein interactions. . . . Therefore p85 mediates the specificity of association of PtdIns 3-kinase with other proteins.") Thus, Kapeller teaches away from Applicant's claimed fusion constructs exhibiting PI 3-kinase activity regardless of membrane localization because Kapeller expressly implicates protein-protein interactions as an additional requirement for PI 3-kinase activity.

Varticovski and Aronheim do not directly address the teaching away by Kapeller. Varticovski discloses the importance of plasma membrane localization to PI 3-kinase activity.

Aronheim discloses that myristoylation and farnesylation signals may be sufficient for membrane targeting of certain heterologous proteins. However, neither teaches that membrane localization of a PI 3-kinase fusion construct with or without a membrane targeting domain, such as that of the claimed polynucleotide fusion constructs, will result in a catalytically active PI 3-kinase. In fact, Aronheim teaches the opposite, stating that localization to the plasma membrane alone may not be sufficient to produce a catalytically active PI 3-kinase, and that activation of PI 3-kinase may involve "[m]ore complex mechanisms" than activation of the proteins examined, including conformational changes *(citing* Susa *et al., J. Biol. Chem. 267:22951-22956),* tyrosine phosphorylation *(citing* Hayashi *et al., J. Biol. Chem. 267:22575-22580),* and dephosphorylation of autophosphorylated serine/threonine sites on p110 (citing Dhand *et al., EMBO J. 13:522-533).* (Aronheim, at page 949, left column, paragraph 2.) Aronheim further states that "[t]he contribution of these mechanisms to PI3K activation *in vivo* is not known."

Thus, given Kapeller's disclosure that other functional domains of p85 not found in the claimed invention might be important to PI 3-kinase activity, and Aronheim's disclosure of all of the above-cited unknowns and "[m]ore complex mechanisms," the combination of Kapeller, Varticovski, and Aronheim not only teach away from the Applicant's claimed invention, but fail to suggest or provide a reasonable expectation of success that the Applicant's PI 3-kinase fusion constructs (or any derivative or mutein thereof), regardless of the presence of a membrane targeting domain, would encode an active PI 3-kinase. *See Amgen v. Chugai,* 18 USPQ2d at 1022 ("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.").

The combined disclosures of Hu, Kapeller, Varticovski, and Aronheim fail to reach the instant invention. The withdrawal of this basis for rejection is therefore respectfully requested.

Klippel (1994), Kapeller, Varticovski, and Aronheim

Claims 1, 4, and 8 have been rejected under §103(a) as unpatentable over Klippel *et al.*, Mol. Cell. Biol., 14(4):2675-2685 (1994) (hereinafter "Klippel (1994)") in view of Kapeller, Varticovski, and Aronheim.

The Examiner cited Klippel (1994) for disclosing "constructs encoding the p110 and p85 subunits of PI 3-kinase, as well as their fragments, including the iSH2 portion of the p85 subunit." The Examiner also cited Klippel (1994) for disclosing that the complex containing either the recombinant full length p85 or the iSH2 containing p85 fragments with the recombinant full length p110 exhibits PI 3-kinase activity in COS cells co-expressing these recombinant constructs. The Examiner admitted, however, that Klippel does not teach constructs comprising DNA encoding a membrane targeting sequence.

Kapeller was cited for disclosing that "localization of PI 3-kinase to the plasma membrane is expected to increase the 3-kinase activity, since it brings the enzyme into closer contact with its substrates." Varticovski was cited for disclosing that "PI 3-kinase must be localized to a membrane to work efficiently." Aronheim was cited for disclosing "methods for localizing proteins to membranes by addition of myristoylation, farnesylation and palmitoylation signal sequences." On this basis, the Examiner then concluded that it would have been obvious at the time of the invention to modify the constructs of Klippel (1994) by further adding DNA encoding membrane localization sequences as taught by Kapeller, Varticovski, and Aronheim.

Applicant respectfully disagrees with the Examiner's position. At the time of the invention, one of ordinary skill in the art would not equate the *in vivo* co-expression of PI 3-kinase subunits, which assumes conformation that allows them to specifically bind to one another, with that which occurs "when the two subunits are co-expressed [end to end] as a fusion protein." In particular, Klippel (1994) discloses that the binding of p85 to p110 is "necessary, but not sufficient for PI 3-kinase activity." See Klippel (1994), at page 2680, right column, paragraph 1. Klippel (1994) discloses that other mechanisms besides the binding of p85 to p110

may be involved in PI 3-kinase activation, *e.g.*, conformational changes induced by p110-p85 complex formation. (Klippel (1994), at page 2683, right column, paragraph 1.) In particular, Klippel (1994) discloses that "p85 bound to the p110 terminus may assist in the proper folding of the p110 catalytic domain in a co- or post-translational manner, thus acting as a p110-specific chaperone." (Klippel (1994), at page 2883, left hand column, first paragraph.). The teachings of Klippel (1994) do not teach that association *in vitro* of the two subunits produced separately produce an active enzyme. Thus, one of ordinary skill in the art would appreciate the importance of "conformational changes" following the binding of p85 to p110 to PI 3-kinase activation. However, in the absence of actual testing, one of ordinary skill in the art would not have a reasonable expectation that p85 and p110 subunits tethered together by a glycine linker would have the appropriate spatial and conformational relationships to allow them to bind together to form a p85/p110 complex or that the resulting complex would have PI 3-kinase activity because (1) the glycine linker could prevent the conformational changes otherwise induced by the binding of p85 to p110 and otherwise required for proper folding of the p110 catalytic domain, and/or (2) the glycine linker could constrain the p85 and p110 subunits from properly interacting with other proteins that were believed to be necessary for, but not sufficient to activate PI 3-kinase. Thus, equating the *in vivo* co-expression of PI 3-kinase subunits with that which occurs when the two subunits are co-expressed as a fusion protein is speculation that is unsupported by the prior art, but found only in the Applicant's disclosure. Accordingly, Klippel (1994) teaches away from any expectation that the claimed polynucleotide fusion constructs would encode a protein forming a p85/p110 complex having PI 3-kinase activity. *In re Fine, 5* USPQ2d 1596, 1599 (Fed. Cir. 1988) ("[e]rror to find obviousness where the references diverge and teach away from the invention at hand."). The withdrawal of this basis for rejection is respectfully requested.

Notwithstanding the teaching away of Klippel (1994), the Examiner has failed to make a *prima facie* case of obviousness against the present invention because the remaining cited art also teaches away from the claimed invention by disclosing that other factors, in addition to membrane localization and conformational changes, but not found in the proteins encoded by the present invention, are required for PI 3-kinase activity. As discussed above, Kapeller discloses

that other functional domains of p85, which are not found in the proteins encoded by the claimed invention, may be important for protein-protein interactions and may be required for PI 3-kinase activity *e.g.*, SH2 and SH3 domains. (*See* Kapeller, at page 567, paragraph 2 to page 569, paragraph 1: "The SH2 and SH3 domains of p85 have been implicated in mediating protein-protein interactions...Therefore p85 mediates the specificity of association of PtdIns 3-kinase with other proteins.") Similarly, Aronheim discloses that plasma membrane association of a PI 3-kinase alone may not be sufficient to produce a catalytically active wild-type PI 3-kinase. Aronheim specifically states that activation of PI 3-kinase may involve "[m]ore complex mechanisms" than activation of the proteins examined therein, including conformational changes *(citing* Susa *et al., J. Biol. Chem.* 267:22951-22956), tyrosine phosphorylation *(citing* Hayashi *et al., J. Biol. Chem.* 267:22575-22580), and dephosphorylation of autophosphorytated serine/threonine sites on p110 *(citing* Dhand *et al., EMBO J. 13:522-533)* (Aronheim, at page 949, left column, paragraph 2). Aronheim further states that "[t]he contribution of these mechanisms to PI3K activation *in vivo* is not known" *Id.* Thus, like Klippel (1994), the secondary references disclose that a multiplicity of complex mechanisms and factors other than membrane localization may be required for wild-type PI 3-kinase activity.

Because these cited references disclose that membrane localization alone may not be sufficient to activate wild-type PI 3-kinase, it was even less likely for one of skill in the art to consider that the fusion construct of the claimed invention, which encodes a truncated p85 and only two functional domains of p110, with or without membrane localization signals, would result in a protein having PI 3-kinase activity. As such, the combination of Klippel (1994), Kapeller, Varticovski, and Aronheim, teaches away from the proteins encoded by the PI 3-kinase polynucleotide fusion constructs of the claimed invention and any expectation that they would be active. *See In re Fine, 5* USPQ2d at 1599 ("[E]rror to find obviousness where references 'diverge from and teach away from the invention at hand."). The withdrawal of this basis for rejection is therefore respectfully requested.

Klippel (1994), Kapeller, Varticovski, Aronheim, and Eichner

Claims 2-3 and 5 were rejected under §103(a) as unpatentable over Klippel (1994) in view of Kapeller, Varticovski, and Aronheim, and further in view of USPN 5,665,567 to Eichner *et al.* (hereinafter "Eichner").

Klippel (1994), Kapeller, Varticovski, and Aronheim were applied to claims 1, 4, and 8. Eichner, which teaches a bicistronic vector system, was cited by the Examiner as providing teaching to support nucleotide sequences for the p110 subunit and the p85 subunit (or their mutants) being on the same construct.

Applicant disagrees with this assessment. Even with the addition of the Eichner reference to show a combination of sequences on the same construct, the deficiencies of the other references has not been overcome. As discussed above, the combination of Klippel (1994), Kapeller, Varticovski, and Aronheim fails to make Applicant's invention obvious. The addition of Eichner's teachings do not change that conclusion.

Klippel (1994) discloses that the binding of p85 to p110 is "necessary, but not sufficient for PI 3-kinase activity." See Klippel (1994), at page 2680, right column, paragraph 1. Klippel (1994) discloses that other mechanisms besides the binding of p85 to p110 may be involved in PI 3-kinase activation, *e.g.,* conformational changes induced by p110-p85 complex formation. (Klippel (1994), at page 2683, right column, paragraph 1.) In particular, Klippel (1994) discloses that "p85 bound to the p110 terminus may assist in the proper folding of the p110 catalytic domain in a co- or post-translational manner, thus acting as a p110-specific chaperone." (Klippel (1994), at page 2883, left hand column, first paragraph.). The teachings of Klippel (1994) do not teach that association *in vitro* of the two subunits produced separately produce an active enzyme. The suggestion of Eichner, as stated by the Examiner, of providing teaching to support nucleotide sequences for the p110 subunit and p85 subunit (or their mutants) being on the same construct, even assuming Applicant agrees with this position, when added to the teachings of Klippel (1994) and the other references similarly does not lead one to a conclusion that an active enzyme

is produced. One of ordinary skill in the art would appreciate the importance of "conformational changes" following the binding of p85 to p110 to PI 3-kinase activation and also that a teaching of the two subunits possibly being on the same construct fails to reach Applicants' invention.

Accordingly, Eichner fails to add the requisite disclosure to Klippel (1994), Kapeller, Varticovski, and Aronheim, which teach away from any expectation of achieving the instant invention. *In re Fine, 5* USPQ2d 1596, 1599 (Fed. Cir. 1988) ("[e]rror to find obviousness where the references diverge and teach away from the invention at hand."). The withdrawal of this basis for rejection is therefore requested.

USPN 6,300,111 B1, Kapeller, Varticovski, and Aronheim

Claims 1-9 were rejected under §103(a) as being obvious over USPN 6,300,111 B1 in view of Kapeller, Varticovski, and Aronheim. Additionally, claims 1-9 of the instant application were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of USPN 6,300,111 B1, in view of Kapeller, Varticovski, and Aronheim.

USPN 6,300,111 B1 was cited by the Examiner to teach an expression vector comprising a DNA encoding a constitutively active phosphatidylinositiol 3-kinase polypeptide, wherein the polypeptide comprises a p85 subunit iSH2 domain sequence or a conservatively modified variant thereof linked at the carboxy-terminus by a linker to the amino-terminus of a p110 subunit or a conservatively modified variant thereof and a cell containing the expression vector. The Examiner admitted that USPN 6,300,111 B1 does not teach that the expression vector further comprises a nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence at the 5' end or 3' end of the DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide.

As before, Kapeller is cited for disclosing that "localization of PI 3-kinase to the plasma membrane" brings the enzyme into closer contact with its substrates. Varticovski is cited for

disclosing that "PI 3-kinase must be localized to a membrane to work efficiently." Aronheim is cited for disclosing "methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for myristoylation, farnesylation, and palmitoylation

Applicant respectfully disagrees with the Examiner's position and asks that the rejections based on USPN 6,300,111 B1, *i.e.*, both the § 103(a) obviousness and the non-statutory obviousness-type double patenting, be withdrawn. When the references are considered as a whole, they do not make obvious Applicant's invention.

As noted above, Kapeller, Varticovski, and Aronheim teach away from the claimed invention by disclosing factors, in addition to membrane localization, that are not found in the present invention but that are required for PI 3-Kinase activity. Kapeller, Varticovski, and Aronheim, as a whole, teach away from any polynucleotide encoding any single protein, including a fusion protein, that would have PI 3-kinase activity due to membrane localization alone. Kapeller teaches away from the claimed polynucleotide fusion constructs by disclosing that other functional domains of p85, which are not components of the claimed polynucleotide fusion constructs (nor encoded by them), may be important for protein-protein interactions and may be required for PI 3-kinase activity, *e.g.*, SH2 and SH3 domains fall into this category. (Kapeller, at page 567, paragraph 2 to page 569, paragraph 1: "The SH2 and SH3 domains of p85 have been implicated in mediating protein-protein interactions. . . . Therefore p85 mediates the specificity of association of PtdIns 3-kinase with other proteins.") Thus, Kapeller teaches away from Applicant's claimed fusion constructs exhibiting PI 3-kinase activity regardless of membrane localization because Kapeller expressly implicates protein-protein interactions as an additional requirement for PI 3-kinase activity.

Varticovski and Aronheim do not overcome the teaching away by Kapeller. Varticovski discloses the importance of plasma membrane localization to PI 3-kinase activity. Aronheim discloses that myristoylation and farnesylation signals may be sufficient for membrane targeting of certain heterologous proteins. Neither, however, teaches that membrane localization of a PI 3-kinase fusion construct with or without a membrane targeting domain, such as that of the claimed

polynucleotide fusion constructs, will result in a catalytically active PI 3-kinase. Aronheim actually teaches the opposite, stating that localization to the plasma membrane alone may not be sufficient to produce a catalytically active PI 3-kinase, and that activation of PI 3-kinase may involve "[m]ore complex mechanisms" than activation of the proteins they examined, including conformational changes *(citing* Susa *et al., J. Biol. Chem. 267:22951-22956),* tyrosine phosphorylation *(citing* Hayashi *et al., J. Biol. Chem. 267:22575-22580),* and dephosphorylation of autophosphorylated serine/threonine sites on p110 (citing Dhand *et al., EMBO J. 13:522-533).* (Aronheim, at page 949, left column, paragraph 2.) Aronheim further states that "[t]he contribution of these mechanisms to PI3K activation *in vivo* is not known."

Thus, given Kapeller's disclosure that other functional domains of p85 not found in the claimed invention might be important to PI 3-kinase activity, and Aronheim's disclosure of all of the above-cited unknowns and "[m]ore complex mechanisms," the combination of Kapeller, Varticovski, and Aronheim not only taught away from the Applicant's claimed invention, but failed to suggest or provide a reasonable expectation of success that the Applicant's PI 3-kinase fusion constructs (or any derivative or mutein thereof), regardless of the presence of a membrane targeting domain, would encode an active PI 3-kinase. USPN 6,300,111 B1, when combined with these references, fails to provide remedy. *See Amgen v. Chugai,* 18 USPQ2d at 1022 ("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.").

The combination of USPN 6,300,111 B1, Kapeller, Varticovski, and Aronheim therefore does not make obvious Applicant's invention. Therefore, Applicant respectfully requests that the rejections be withdrawn.

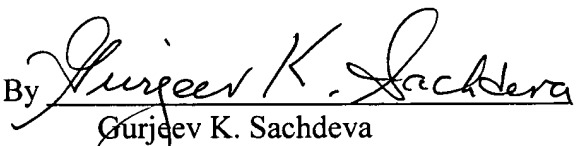
Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: August 28, 2006

By 
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ANNOTATED SHEET

Attorney Docket No. 356000-1650
Title: PI 3-KINASE FUSION MUTANTS AND USES THEREOF
By: KLIPPEL, et al.
Serial No.: 10/601,610
Filed: June 23, 2003



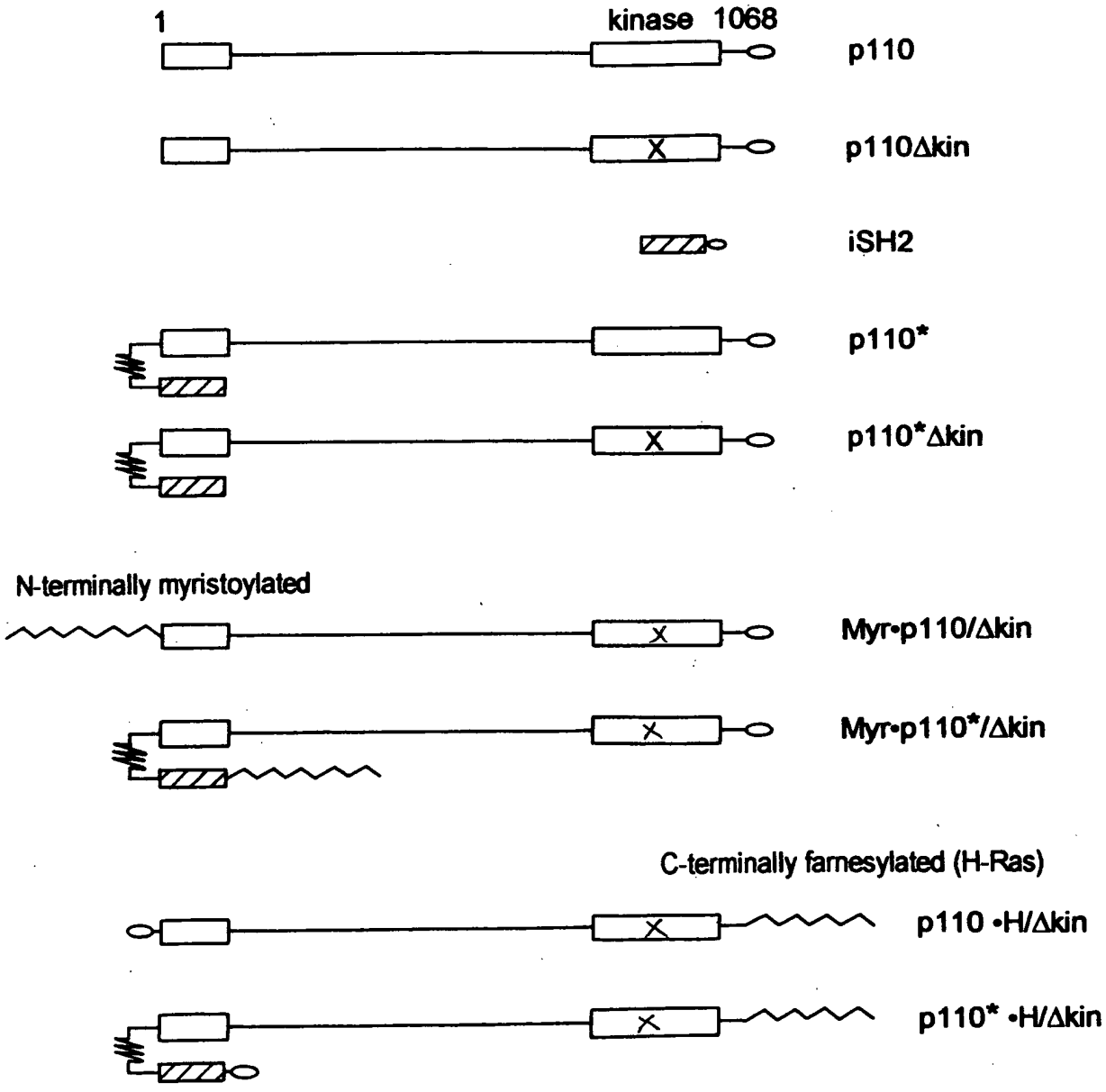


FIG. 1